REMARKS

Claims 95-138 are pending in this application. Applicants have amended claims 96, 100-104, 106, 110-114, 120-124, 126 and 130-135 without prejudice or disclaimer. Claims 136-138 are new. Claim amendments and the new claims are supported by the application as filed, e.g., at page 67, line 23 to page 75, line 5, and Examples 34-37 at pages 98-99. No new matter has been added.

Withdrawn Objections

Applicants thank the Examiner for withdrawing the previously-raised objections to the claims and specification.

Withdrawn Rejections

Applicants also thank the Examiner for withdrawing the previously-pending written description, indefiniteness, double patenting, novelty and obviousness rejections.

Claim Objections

At page 3 of the Office Action, the Office objects to claims 96, 106 and 126. The basis of the objection is not clear. Nonetheless, Applicants have amended claims 96, 106 and 126 and submit that the objections have been obviated.

35 U.S.C. § 112, First Paragraph, Written Description: New Matter

The Office at pages 4-5 rejects claims 100-104, 110-114, 120-124 and 130-135 as allegedly reciting new matter. To expedite prosecution, claims 100-104, 110-114, 120-124 and 130-135 have been amended as indicated herein. These amendments are supported by the application as filed, e.g., Examples 34-37 at pages 98-99. Withdrawal of the rejection is respectfully requested.

35 U.S.C. § 112, First Paragraph, Enablement

The Office acknowledges that four species of infliximab crystals encompassed by the claimed crystals and the methods recited in the instant specification on pages 98-99 are enabled

by the specification. However, the Office rejects claims 95-135 as allegedly lacking enablement (Office Action at pages 9-15).

This rejection is respectfully traversed. Applicants submit that claims 95-135 satisfy the enablement requirement, as the application clearly describes how to practice the claimed subject matter without undue experimentation, see, e.g., pages 60-75 and Examples 34-37 at pages 98-99.

The Office cites the factors enumerated by *In re Wands* 858 F.2d 731 (Fed. Cir. 1988) to support its allegation that the present claims are not enabled. Each of the factors cited by the Office is discussed below.

The breadth of the claims

Contrary to the Office's assertion, Applicants submit that claims are commensurate in scope with Applicants' disclosure. The claims are drawn to infliximab crystals and methods of crystallizing infliximab. The specification at pages 60-75 describes embodiments that provide methods of producing antibody crystals and formulations and compositions comprising such crystals. Further, the specification at pages 98-99 provides examples that teach methods of infliximab crystallization.

As stated in the MPEP § 2164.08:

> Nevertheless, not everything necessary to practice the invention need be disclosed. In fact, what is well-known is best omitted. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991). All that is necessary is that one skilled in the art be able to practice the claimed invention, given the level of knowledge and skill in the art.
>
> Claims are not rejected as broader than the enabling disclosure under 35 U.S.C. 112 for noninclusion of limitations dealing with factors which must be presumed to be within the level of ordinary skill in the art; the claims need not recite such factors where one of ordinary skill in the art to whom the specification and claims are directed would consider them obvious. *In re Skrivan*, 427 F.2d 801, 806, 166 USPQ 85, 88 (CCPA 1970).

Thus, given the knowledge and skill in the art, the breadth of the claims is no broader than that supported by the specification.

The nature of the invention

The invention is related to crystals of infliximab. The invention is also related to methods of crystallizing infliximab.

The Office alleges that "the ability to crystallize a given antibody (or protein) was, at the least, challenging to a skilled artisan as even minor alterations in the conditions of crystallization could result in failure to form a crystal of infliximab" (pages 11-12). Applicants respectfully disagree. It appears that the Office's position stems from concerns that can arise in preparing single large crystals for X-ray crystallographic studies. However, the claimed invention is not limited to crystallization for X-ray crystallographic structural studies. The application provides numerous examples demonstrating that infliximab was successfully crystallized under a wide-range of conditions. Thus, this factor argues in favor of patentability.

The state of the prior art; the level of one of ordinary skill; and the level of predictability in the art.

The Office alleges that "the quantity of experimentation would be considerable because the smallest change in any parameter in crystallizing a protein/antibody can have enormous consequences" and "crystallizing proteins is an extremely tenuous science" (Office Action at page 12). The Office cites several references in support of its position.

Applicants respectfully disagree. The Office's position and the references cited by the Office essentially relate to the field of protein crystallization for x-ray crystallographic studies. However, the claimed subject matter is not so limited.

The Office Action alleges that "specific crystallization conditions (e.g., temperature, buffer, salt, protein concentration etc.) are needed for each protein and/or antibody" and cites Weber (Methods in Enzymology, 276:13-22, 1997) in support of its position. However, Weber is drawn to the preparation of crystals for structural studies: "Crystallographic structure determination begins with growth of a suitable crystal" (page 13, first paragraph of Introduction). Also, page 21, first paragraph of Conclusion states "Crystallization of a macromolecule in a form suitable for X-ray diffraction studies involves optimization of many solution parameters."

Drenth ("Principles of Protein X-Ray Crystallography", 2nd Edition, Springer-Verlag New York Inc., Chapter 1, 1999) is also drawn to the preparation of crystals for structural studies.

Klyushnichenko (Curr. Op. Drug Discovery, 6(6):848-854, 2003) describes analytical-scale high-throughput screening (HTS) for X-ray crystallographic studies. For example, page 848, right column, last paragraph, states "Crystallization of proteins at small scale is used to obtain a structure for X-ray diffraction analysis and for studying optical, spectroscopic, electrical, thermal and mechanical viscoelastic properties." (internal citation omitted)

In contrast, the present application is not necessarily drawn to crystals for X-ray crystallographic structural studies, which require crystals having large size and high quality.

The standard for determining whether the specification meets the enablement requirement is whether the experimentation needed to practice the invention is undue. The claimed invention must be enabled so that any person skilled in the art can make and use the invention without undue experimentation. MPEP § 2164.01. The test of enablement is not whether any experimentation if necessary, but whether, if experimentation is necessary, it is undue. Id. The application as filed provides guidance and teachings demonstrating that infliximab crystals can be prepared under a variety of conditions. See, e.g., page 67, line 23 to page 75, line 5. Thus, these factors argue strongly in favor of patentability.

The amount of direction provided by the inventor; the existence of working examples

The Office alleges that the specification discloses "only four working examples of the claimed crystal of infliximab and the method of crystallization thereof " and "other than these four working examples, the specification and prior art fail to provide guidance for altering the crystallization conditions for crystallizing infliximab".

As stated in MPEP § 2164.02, "An Applicant need not have actually reduced the invention to practice prior to filing" and "The specification need not contain an example if the invention is otherwise disclosed in such manner that one skilled in the art will be able to practice it without undue amount of experimentation. *In re Borkowski*, 422 F.2d 904, 908, 164 USPQ 642, 645 (CCPA 1970)".

Yet not only have Applicants provided actual working examples showing the preparation of infliximab crystals (see, e.g., Examples 34-37), the specification is also replete with guidance as to how to crystallize infliximab. See, e.g., page 67, line 23 to page 75, line 5.

Thus, the guidance and working examples in the specification are sufficient, and these factors support enablement.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure

The fact that some experimentation may be necessary does not mandate a conclusion that the experimentation required for such process is necessarily undue, as set forth in *Wands*, 858 F. 2d 731. As stated in the MPEP § 2164.06:

> "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.'" *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)). Time and expense are merely factors in this consideration and are not the controlling factors. *United States v. Telectronics Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046(1989).

In light of the teachings and examples provided by the application, undue experimentation would not be required to practice the claimed invention. This factor also supports enablement.

The Office's analysis must consider all the evidence related to each of these factors, and any conclusion of nonenablement must be based on the evidence as a whole. *In re Wands*, 858 F.2d 731, 740, 8 USPQ2d 1400, 1407 (Fed. Cir. 1988). In view of the evidence regarding each of the above *Wands* factors, at the time of filing, the application was sufficient to teach one of ordinary skill in the art how to make and use the full scope of the claimed invention without undue experimentation. Applicants therefore respectfully request that the rejection under 35 U.S.C. § 112, First Paragraph, for lack of enablement, be withdrawn.

35 U.S.C. § 112, First Paragraph, Written Description

The Office acknowledges that Applicants were in possession of four species of infliximab crystals encompassed by the genus of claimed crystals and the methods recited in the instant specification on pages 98-99. However, the Office rejects claims 95-135 as allegedly lacking written description (Office Action at pages 5-8).

This rejection is respectfully traversed.

Applicants submit that claims are commensurate in scope with Applicants' disclosure. Claims 95, 105, 115 and 125 are drawn to infliximab crystals comprising infliximab and (a) ethoxyethanol, lithium sulfate, and Tris buffer; (b) PEG-400, lithium sulfate, and Tris buffer; (c) PEG MME 550, calcium chloride, and Tris HCl buffer; or (d) PEG 300, Tris buffer, PEG 8000, and glycerol. Claims 97, 107, 117 and 127 are directed to methods of crystallizing infliximab. Dependent claims 96, 99, 106, 109, 116, 119, 126 and 129 specify the pH of the Tris buffer. Dependent claims 98, 108, 118 and 128 require the crystallization method to be performed at particular temperature. Dependent claims 100-104, 110-114, 120-124 and 130-135 recite the concentration of each component in the crystallization solution. The specification at pages 60-75 describes embodiments that provide methods of producing antibody crystals and formulation and compositions comprising such crystals. Further, the specification at pages 98-99 provides examples that teach methods of infliximab crystallization. In view of the examples and guidance provided in the application which demonstrate that Applicants used a variety of conditions to successfully prepare infliximab crystals, Applicants submit that possession of the claimed subject matter is clear.

Further, as stated in MPEP § 2163(II)(3)(a)(ii):

> The issue is whether a person skilled in the art would understand applicant to have invented, and been in possession of, the invention as broadly claimed. In *LizardTech*, claims to a generic method of making a seamless discrete wavelet transformation (DWT) were held invalid under 35 U.S.C. 112, first paragraph **because the specification taught only one particular method for making a seamless DWT and there was no evidence that the specification contemplated a more generic method**. (emphasis added)

As discussed above, the application sets forth multiple ways of preparing infliximab crystals (see, e.g., Examples 34-37). Further, the application contemplates multiple and more

generic infliximab crystals and methods of preparing infliximab crystals. See, e.g., page 67, line 23 to page 75, line 5. Thus, a person skilled in the art would understand Applicants to have invented, and been in possession of, the invention as broadly claimed.

Applicants respectfully submit that the application clearly demonstrates that Applicants were in possession of the claimed subject matter. For at least these reasons, Applicants respectfully request that the Office reconsider and withdraw the written description rejection under 35 U.S.C. §112, First Paragraph.

CONCLUSION

Applicants respectfully submit that all claims are in condition for allowance in light of the amendments and arguments presented herein. Applicants do not concede any positions of the Examiner that are not expressly addressed above, nor do Applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. Please charge any deficiency to Deposit Account No. 50/2762.

Respectfully submitted,

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